PCT/EP 03/07612

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I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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Signed Stephen Hordley

Dated 26 June 2003

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15JUL02 E73306 -1 D01030
P01/7700 0.00-0216224.6

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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1. Your Reference — PF4877

2. Patent application number *(The Patent office will fill in this part)* — 0216224.6

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GLAXO GROUP LIMITED
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~~TW8 9GS~~

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GREENFORD
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UB6 0NN

Patents ADP number *(if you know it)* 07358700 6

If the applicant is a corporate body, give the country/state of its corporation

4. Title of the invention — COMPOUNDS

9020/77 10.10.02

5. Name of your agent *(if you know one)* — JANETTE Y ROWDEN

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Patents ADP number *(if you know it)* 08366817001

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(If you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

YES

See note (d))

Patents Form 1/77

9. For the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	48
Claim(s)	3
Abstract	2
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

Signature **JANETTE Y ROWDEN**
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

LYNNE SAWKINS
020 8047 4461

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a) *Notes*

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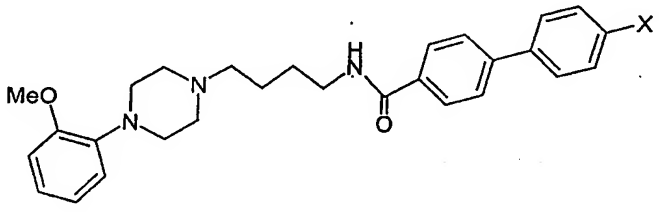
Therapeutic Aryl Piperidine Derivatives

This invention relates to novel compounds which up-regulate LDL receptor (LDL-r) expression and to processes for their preparation, pharmaceutical compositions containing them and their medical use. More particularly, this invention relates to novel aromatic piperidines and their use in therapy.

Epidemiological studies have clearly demonstrated the correlation between reduction in plasmatic LDL cholesterol and the benefit on cardiovascular events including mortality. LDL cholesterol is eliminated from plasma by specific binding to LDL-r expressed by the liver. Regulation of LDL-r expression occurs in the liver and is mainly dependent on intracellular cholesterol concentration. Increasing free cholesterol concentration leads to a reduced LDL-r expression through a mechanism involving transcriptional factors. Counteracting with this process is expected to up-regulate LDL-r expression in the liver and to increase the clearance of LDL cholesterol.

International Patent Application Number PCT.EP00.06668 concerns the novel use of the SREBP-cleavage activating protein (SCAP) in a screening method, and two compounds are disclosed, namely 4-(4-chloro-benzoylamino)-N-{4-[4-(2-ethoxy-4-ethyl-phenyl)-piperidin-1-yl]-butyl}-benzamide and 4-(4-Benzoyl)-N-{4-[4-(4-isopropyl-2-methoxy-phenyl)-piperidin-1-yl]-butyl}-benzamide hydrochloride, which do not form part of the present invention.

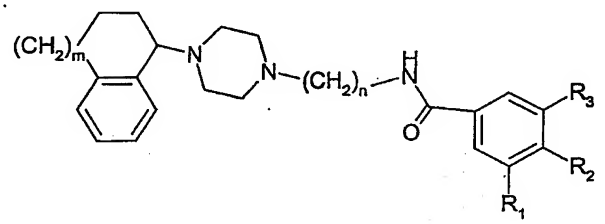
Another publication, Bioorganic and Medicinal Chemistry Letters Vol. 5, 3, 219-222, 1995 discloses compounds having the general formula (A)



A

where X may be COMe, SO_2Me and NH_2, as having high affinity for the dopamine D_3 receptor and postulates their use in CNS disorders, particularly psychiatric illness. The compound of formula A where X is COMe is also disclosed in J.Pharmacol. Exp. Ther. 287; 1 1998 187-197 and Bioorganic and Medicinal Chemistry Letters Vol. 7, 15, 1995-1998, 1997, again as being useful in treating CNS disorders. It will be noted that the examples of the present invention differ from those of formula (A) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

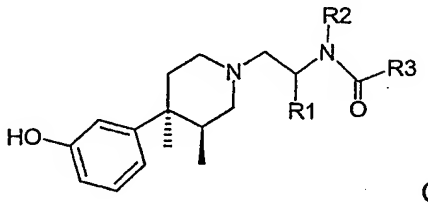
Journal Of Medicinal Chemistry, Vol. 40, 6, 952-960, 1997 discloses compounds of formula (B)



B

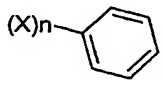
where m=0,1 or 2; n=2 or 3; R_1 and R_3= H or OMe and R^2 may be Ph, as selective 5-HT_{1A} receptor ligands having CNS activity. It will be noted that the examples of the present invention differ from those of formula (B) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

International Patent Application Publication Number WO99/45925 discloses compounds of formula (C)



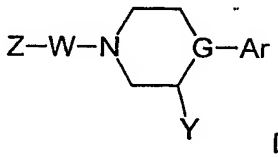
C

where R^1 may be hydrogen, R^2 may be hydrogen and R^3 may be a group



where X may be an aryl group and n may be 1. Specifically disclosed are compounds where the group COR^3 is formed from 2- and 4- biphenyl carboxylic acid and R^1 and R^2 are methyl or hydrogen respectively. The utility of the compounds is as opioid receptor binding agents which may be useful as analgesics. The substitution on the 3- and 4- positions of the piperidine ring leave the compounds of this publication outside the scope of the present invention. Furthermore, the utility disclosed is different.

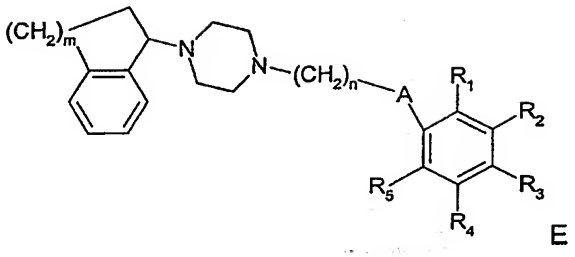
International Patent Application Publication Number WO98/37893 discloses compounds of formula (D)



D

where Ar may represent an optionally substituted phenyl or naphthyl, G may be N or CH_2 (*sic*), W may be an optionally substituted alkylene, Y may be hydrogen and Z may represent a group R_4CONR_5, where R_4 may be an optionally substituted phenyl and R_5 may be hydrogen. These compounds are described as being D2 receptor antagonists useful in the treatment of CNS disorders such as Parkinson's Disease. None of the compounds specifically disclosed fall within the scope of the present invention and the disclosed utlity is different.

International Patent Application Publication Number WO9402473 discloses compounds of formula (E)



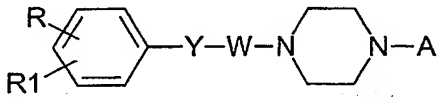
E

where A may be NHCO or CONH; R_1-R_5 may be hydrogen or a benzene ring, m may be 1-3 and n may be 1-3. Specifically disclosed are the following compounds:

No.	A	n	m	R_1	R_2	R_3	R_4	R_5
5	NHCO	2	1	H	H	Ph	H	H
12	NHCO	2	2	H	H	Ph	H	H
19	NHCO	2	3	H	H	Ph	H	H

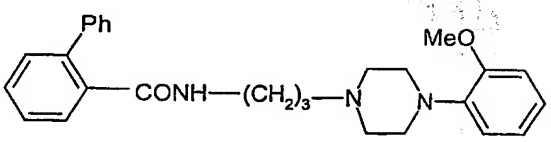
The compounds are described as 5HT-1A agonists having CNS activity and may be used as anti-depressants, anti-hypertensive, analgesics etc. It will be noted that the examples of the present invention differ from those of formula (E) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

International Patent Application Publication Number WO99/45925 discloses compounds of formula (F)



F

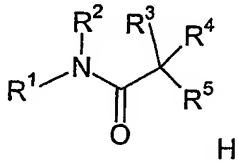
where A may represent a substituted phenyl group, W represents a linear or branched alkylene group having from 2 to 6 carbon atoms; Y may represent a group NHCO or CONH; and R may be a substituted phenyl group. Particularly disclosed is the compound G



(G)

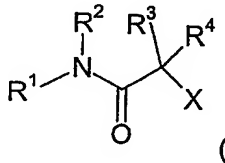
These compounds are described as being α1A-adrenergic receptors useful in the treatment of contractions of the prostate, urethra and lower urinary tract, without affecting blood pressure. It will be noted that the examples of the present invention differ from those of formula (G) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

International Patent Application Publication Number WO98/35957 describes compounds of formula (H)



H

wherein R1-R5 are each individually selected from the group of substituents including hydrogen, halogen, hydroxyl, thiol, lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkylalkenyl, alkylalkynyl, alkoxy, alkylthio, acyl, aryloxy, amino, amido, carboxyl, aryl, substituted aryl, heterocycle, heteroaryl, substituted heterocycle, heteroalkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, alkylcycloheteroalkyl, nitro and cyano. Specifically disclosed compounds are those formed by the N-alkylation of a a substituted piperidine or piperazine with a group (J)

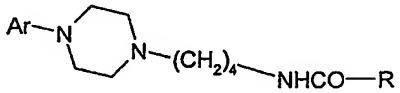


(J)

where X is a leaving group. None of the compounds specifically disclosed fall within the scope of the present invention and the invention is in no way suggested by the disclosure. The compounds are said to be of use as NPY Y5 receptor antagonists in the treatment of obesity, bulemia and related disorders

and NPY Y5 receptor inhibition related disorders such as memory disorders, epilepsy, dyslipidemia and depression. US Patent no. 6,048,900, published after the priority date of the present invention discloses the same information.

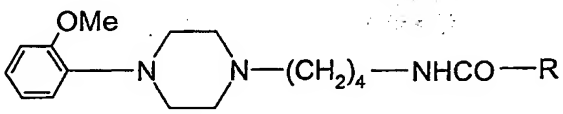
Journal Of Medicinal Chemistry, Vol. 31, 1968-1971, 1988 discloses certain aryl piperazines compounds, which fall outside the present invention, as 5HT-1a Serotonin Ligands as potential CNS agents. Specifically disclosed are compounds of formula (K)



(K)

where Ar=Ph and R = Ph, Ar= 2-OMePh and R =Ph and Ar=2-pyrimidyl and R=Ph.

Journal Of Medicinal Chemistry, Vol. 34, 2633-2638, 1991 discloses aryl piperazines having reduced α1 adrenergic affinity. Specifically disclosed is the compound (L)

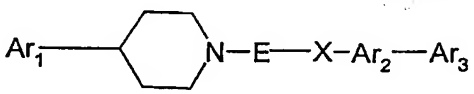


(L)

where R is 4-(BnO)-phenyl, which falls outside the scope of the present invention.

The present invention provides aryl piperidine derivatives which are particularly useful in treating cardiovascular disorders associated with elevated levels of circulating LDL-cholesterol.

Thus, the present invention provides, as a first aspect, a compound of formula (I)



(I)

wherein

Ar_1 represents

(i) phenyl, naphthyl, or phenyl fused by a C_{3-8}cycloalkyl , or

(ii) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, provided that at least one ring is aromatic,

where Ar_1 optionally bears 1-4 groups independently represented by R^1 ;

R^1 is selected from halogen, -O-(C_{0-4} alkylene)-R^2 or –(C_{0-4}alkylene)-R^2, where each alkylene group may additionally incorporate an oxygen in the chain, with the proviso that there are at least two carbon atoms between any chain heteroatoms ;

R^2 represents

(i) hydrogen, C_{1-4} perfluoroalkyl, C_{1-4}perfluoroalkoxy,

(ii) phenyl, phenyl fused by a C_{3-8}cycloalkyl , naphthyl or a 5- or 6-membered heteroaromatic group, optionally substituted by one or two groups independently selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino and di-C_{1-4} alkylamino,

(iii) C_{3-8}cycloalkyl or a monocyclic heterocyclyl radical containing a total of 3-7 ring atoms, wherein said radical contains a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein said radical may be independently saturated, partially unsaturated, or aromatic, and where the C_{3-8}cycloalkyl or a monocyclic heterocyclyl may bear one or two groups independently selected from

halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino and di-C_{1-4} alkylamino, or

(iv) amino, C_{1-4} alkylamino or di-C_{1-4}alkylamino;

Ar_2 represents phenyl or a 5-6 membered heteroaromatic group or a bicyclic heteroaromatic group, where each group is substituted by 1-4 groups independently selected from the group consisting of: $(CH_2)_nOH$ and $C(O)O(CH_2)_mCH_3$, wherein n is 1-4 and m is 0-4;

Ar_3 represents

(i) phenyl, naphthyl, or phenyl fused by a C_{3-8}cycloalkyl,

(ii) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, providing that at least one ring is aromatic,

where Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: hydroxy, alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkenyloxy, C_{1-4} perfluoroalkoxy, C_{1-4} acylamino or an electron withdrawing group selected from the list consisting of: nitrile, nitro, C_{1-4}, C_{1-4} perfluoroalkyl, C_{1-4} acyl , C_{1-4} alkoxycarbonyl, aminocarbonyl, C_{1-4} alkylaminocarbonyl; di-C_{1-4} alkylaminocarbonyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylaminosulfonyl and di-C_{1-4} alkylaminosulfonyl, C_{1-4} alkylsulfonyl and C_{1-4}alkylsulfoxy;

E represents -C_{1-6} alkylene-;

X represents -CON(H or C_{1-4}alkyl)- or –N(H or C_{1-4}alkyl)CO-;

or a physiologically acceptable prodrug, salt or solvate thereof.

As used herein the term "physiologically acceptable" means a compound which is suitable for pharmaceutical use.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable inorganic acids for example, hydrochlorides, hydrobromides or sulphates, or with pharmaceutically acceptable organic acids for example mesylates, lactates and acetates. More suitably, a physiologically acceptable salt of the compounds of general formula (I) is a mesylate salt.

The solvates may, for example, be hydrates.

In addition, prodrugs are also included within the context of this invention. Prodrugs are any covalently bonded carriers that release a compound of structure (I) in vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or in vivo, yielding the parent compound. Prodrugs include, for example, compounds of this invention wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxy, amine or sulfhydryl groups. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of alcohol, sulfhydryl and amine functional groups of the compounds of structure (I). Further, in the case of a carboxylic acid (-COOH), esters may be employed, such as methyl esters, ethyl esters, and the like.

References hereinafter to a compound according to the invention include compounds of formula (I) and their physiologically acceptable prodrugs, salts and solvates.

Referring to the general formula (I), alkyl, alkylene and alkoxy include both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl and ethyl groups, examples of alkylene groups include methylene and ethylene groups, whilst examples of alkoxy groups include methoxy and ethoxy groups.

Referring to the general formula (I), alkenyl includes both straight and branched chain saturated hydrocarbon groups containing one double bond. Examples of alkenyl groups include ethenyl or n-propenyl groups.

Referring to the general formula (I), acyl refers to aliphatic or cyclic hydrocarbons attached to a carbonyl group through which the substituent bonds, such as acetyl.

Referring to the general formula (I), phenyl fused by a C_{3-8}cycloalkyl includes bicyclic rings such as 1,2,3,4-tetrahydronaphthyl, which, for the avoidance of doubt, is linked to the rest of the molecule through the aromatic ring.

Referring to general formula (I), a halogen atom includes fluorine, chlorine, bromine or iodine.

Referring to the general formula (I), C_{1-3}perfluoroalkyl and C_{1-3}perfluoroalkoxy includes compounds which the hydrogens have been partially or fully replaced by fluorines, such as trifluoromethyl and trifluoromethoxy or trifluoroethyl.

Referring to the general formula (I), a 5-6 membered heteroaromatic group includes a single aromatic ring system containing at least one ring heteroatom independently selected from O, N and S. Suitable examples include pyridyl and thiazolyl.

Referring to the general formula (I), a C_{3-8} cycloalkyl group means any single carbocyclic ring system, wherein said ring is fully or partially saturated. Suitable examples include cyclopropyl and cyclohexyl groups.

Referring to the general formula (I), a 3-7 membered heterocycloalkyl group means any single ring system containing at least one ring heteroatom independently selected from O, N and S, wherein said ring is fully or partially saturated.

Preferably, Ar_1 represents phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indole, benzofuran or benzthiophene. More preferably, Ar_1 represents phenyl, 1,2,3,4-tetrahydronaphthyl or indole.

Where Ar_1 is 1,2,3,4-tetrahydronaphthyl, the link to the piperidine ring is preferably through the 2- position of the 1,2,3,4-tetrahydronaphthyl moiety and mono-substitution by R^1 is in the corresponding 1- position.

Where Ar_1 is indole, the link to the piperidine ring is preferably through the 3- position of the indole moiety and mono-substitution by R^1 is in the corresponding 1- position.

Where Ar_1 is naphthyl, the link to the piperidine ring is preferably through the 1- or 2- position of the naphthyl moiety and mono-substitution by R^1 is in either the corresponding 2- or 1- positions respectively.

E is preferably an n-butylene group.

X is preferably a -N(H or C_{1-4} alkyl)CO- group, more preferably an -N(H)CO- group.

Preferably, Ar_2 represents phenyl or a 5-6-membered heteroaromatic group. More preferably Ar_2 represents phenyl, thiazolyl or oxadiazole.

Ar_3 is preferably a phenyl or pyridyl group, suitably 2-pyridyl. Ar_3 is preferably substituted by halogen, e.g. chloro or C_{1-4}perfluoroalkyl, e.g. trifluoromethyl, nitrile, C_{1-4}acyl, e.g. acetyl, or C_{1-4}alkylsulfonyl, e.g. methylsulfonyl.

When Ar_3 is phenyl, para- substitution is preferred.

Particularly preferred compounds of the invention include those in which each variable in Formula (I) is selected from the preferred groups for each variable. Even more preferable compounds of the invention include those where each variable in Formula (I) is selected from the more preferred or most preferred groups for each variable.

The compounds of the invention are inducers of LDL-r expression and are thus of use in the treatment of conditions resulting from elevated circulating levels of LDL-cholesterol.

The ability of the compounds of the invention to induce LDL-r expression by human hepatocytes in vitro is determined using a human hepatocarcinoma cell line, Hep G2, as a model system. A reporter gene assay using the LDL-r promoter in front of the reporter gene Luciferase is used as a primary screen.

The in vivo profile of the compounds is evaluated by oral administration of the compounds of the invention to fat-fed hamsters. Measurements of VLDL/LDL cholesterol and triglycerides upon treatment allow the activity to be determined.

The compounds of the invention are potent and specific inducers of LDL-r expression, which furthermore exhibit good oral bioavailability and duration of action.

Compounds of the invention are of use in the treatment of diseases in which lipid imbalance is important, e.g. atherosclerosis, pancreatitis, non-insulin dependent diabetes mellitus (NIDDM), coronary heart diseases and obesity.
Compounds of the invention are also useful in lowering serum lipid levels, cholesterol and/or triglycerides, and are of use in the treatment of hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia.

The invention therefore provides a compound of formula (I) or a physiologically acceptable prodrug, salt or solvate thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a physiologically acceptable prodrug, salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions resulting from elevated circulating levels of LDL-cholesterol.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of conditions resulting from elevated circulating levels of LDL-cholesterol, comprising administration of an effective amount of a compound of formula (I) or a physiologically acceptable prodrug, salt or solvate thereof.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms. Compounds of formula (I) may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a physiologically acceptable prodrug, salt or solvate thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, transdermal, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such

liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

For transdermal administration the compounds according to the invention may be formulated as creams, gels, ointments or lotions or as a transdermal patch. Such compositions may for example be formulated with an aqueous or oily base with the addition of suitable thickening, gelling, emulsifying, stabilising, dispersing, suspending, and/or colouring agents.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

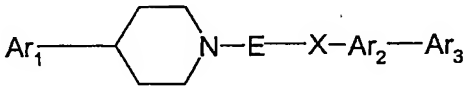
The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

The compositions may contain from 0.1% upwards, e.g. 0.1 - 99% of the active material, depending on the method of administration. A proposed dose of the compounds of the invention is 0.25mg/kg to about 125mg/kg bodyweight per day e.g. 20mg/kg to 100mg/kg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.

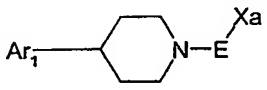
The compounds of formula (I) may, if desired, be administered with one or more therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art. For example, the compounds of formula (I) may be administered in combination with an HMG CoA reductase inhibitor, an agent for inhibition of bile acid transport or fibrates.

A compound of formula (I), or a physiologically acceptable prodrug, salt, solvate or derivative thereof, may be prepared by the general methods outlined hereafter. In the following description, the groups Ar_1, Ar_2, Ar_3, R^1, R^2, R^3, R^4, E and X are as previously defined for compounds of formula (I), unless specified otherwise.

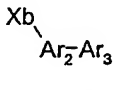


(I)

According to a first general process (A), a compound of formula (I) may be prepared by reaction of a compound of formula (II) with a compound of formula (III)



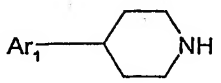
(II)



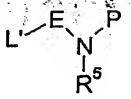
(III)

where Xa and Xb are suitable reactants to form a group X. For example, where X is N(H or C_{1-4} alkyl)CO, Xa is NH_2 or NH(C_{1-4} alkyl) and Xb is COL where L is OH or a suitable leaving group, such as halide. Such a reaction may be effected under standard amide bond-forming conditions, including those described herein.

A compound of formula (II) where Xa is NH_2 or NH(C_{1-4} alkyl), may be prepared by reaction of a compound of formula (IV) with a compound of formula (V)



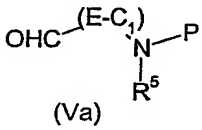
(IV)



(V)

where R^5 represents H or C_{1-4}alkyl, L' is a suitable leaving group, such as halide, and P is any suitable N-protecting group, under standard alkylation conditions, including those described herein, followed by removal of the protecting group under standard conditions.

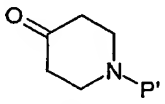
A compound of formula (II) where Xa is NH_2 or NH(C_{1-4} alkyl), may further be prepared by reaction of a compound of formula (IV) with a compound of formula (Va)



(Va)

where R^5 represents H or C_{1-4}alkyl, where E-C_1 ('E minus C_1') means that the chain length of group E is one carbon less than that in the resulting compound (II), and P is any suitable N-protecting group, under standard reductive amination conditions, including those described herein, followed by removal of the protecting group under standard conditions.

A compound of formula (IV) may be prepared by reaction of a compound Ar_1-sal, where sal represents the lithium or magnesium ion of Ar_1, with a compound of formula (VI)



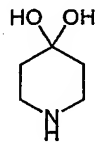
(VI)

where P' represents a suitable N-protecting group, such as acetyl, benzyl or benzyl-4-oxo-1 carboxylate, followed by the steps of dehydration, reduction of the resulting double bond, and finally, removal of the protecting group P' using

standard conditions. Such chemistry has been described, for example, in European Patent Application no. 0630887.

Alternatively, a compound of formula (IV) where Ar_1 is substituted by an activated ortho or para activating group for the reaction centre, Act, e.g. methoxy or hydroxy, may be prepared by reaction of a compound of formula Ar_1-Act, with a compound of formula (VI) under suitable reaction conditions such as e.g. trifluoroborane or acetic acid and aqueous hydrochloric acid, to form a tetrahydropyridyl ring, followed by reduction, e.g. under hydrogenation conditions, of the resulting double bond and finally deprotection of the N-protecting group, P' under standard conditions.

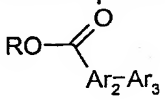
Alternatively, a compound of formula (IV) where where Ar_1 is substituted by an activated ortho or para activating group for the reaction centre, Act, e.g. methoxy or hydroxy, may be prepared by reaction of a compound of formula Ar_1-Act, with a compound of formula (VII)



(VII)

under suitable reaction conditions such as e.g. acetic acid and aqueous hydrochloric acid to form a tetrahydropyridyl ring, followed by suitable N-protection, then reduction, e.g. under hydrogenation conditions, of the resulting double bond and finally deprotection of the N-protecting group.

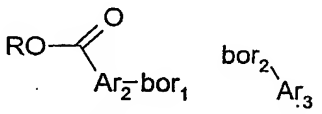
A compound of formula (III) may be prepared by standard methods including, where Xb is CO_2H, deprotection of a compound of formula (X)



(X)

where R is a suitable carboxylic acid protecting group, such as methyl and ethyl.

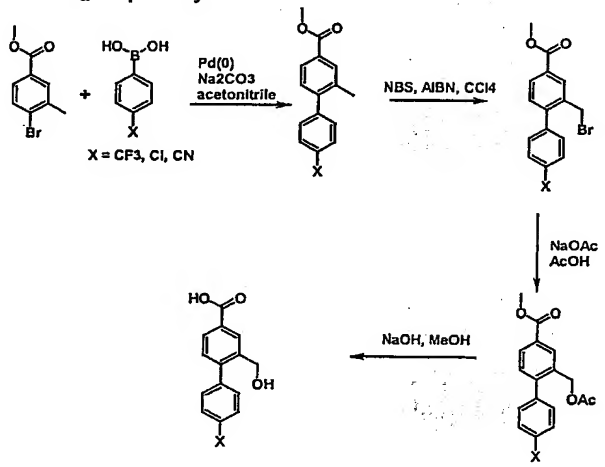
A compound of formula (X) where R is H or a suitable protecting group, may be prepared by reaction of a compound of formula (XI), with a compound of formula (XII)



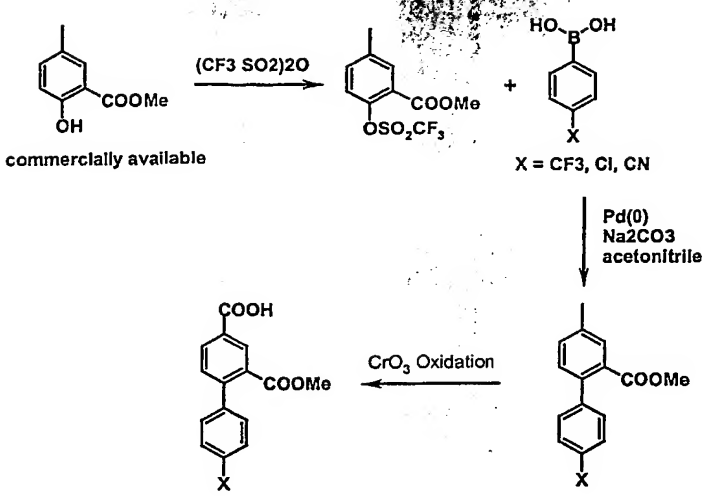
(XI) (XII)

where bor_1 represents a boronic acid group or a halide, e.g. bromide or iodide, and bor_2 represents a suitable boronic acid group or a halide, e.g. bromide or iodide for coupling, under conditions suitable for boronic acid coupling, e.g. using palladium (0) and sodium carbonate.

Schemes 1 and 2 below illustrate examples of the preparation of compounds of formula (X) wherein Ar_2 is phenyl.

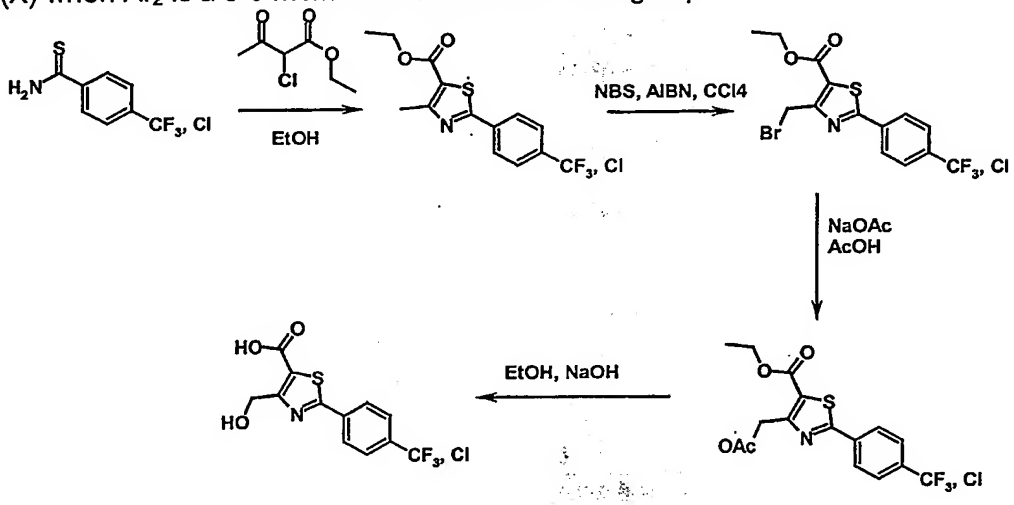


Scheme 1

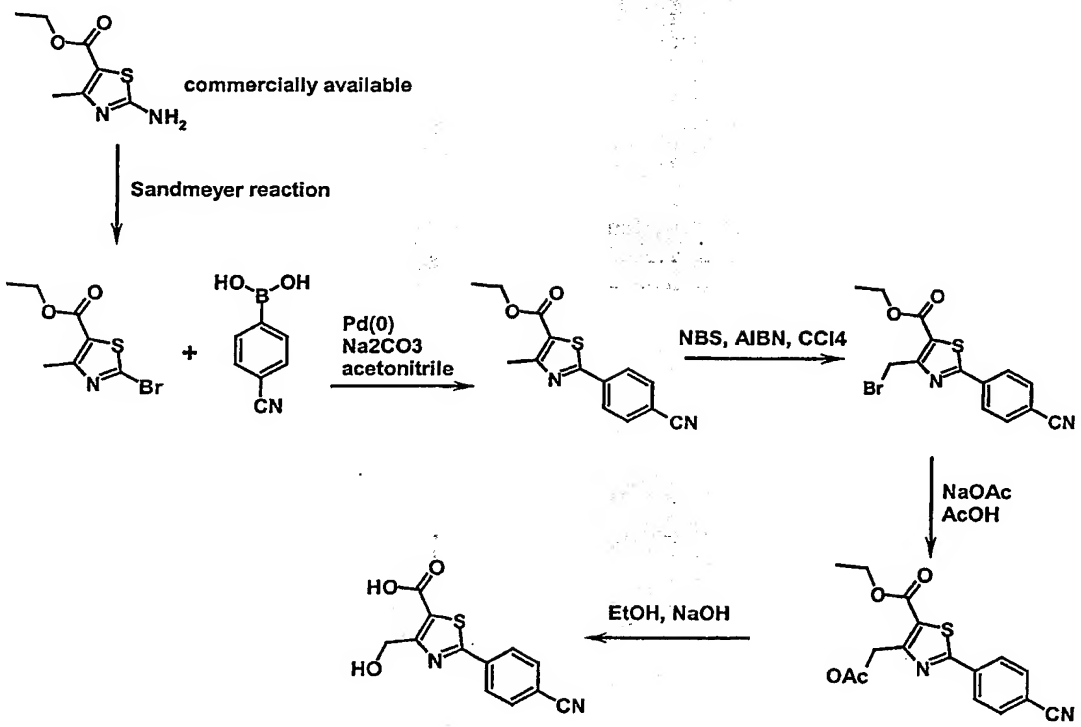


Scheme 2

Schemes 3 and 4 show examples of the preparation of compounds of formula (X) when Ar_2 is a 5-6-membered heteroacromatic group.



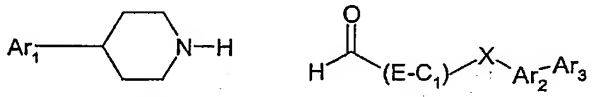
Scheme 3



Scheme 4

It will be apparent to a person skilled in the art that further compounds of formula (X) may be synthesised in an analagous fashion to that illustrated in Schemes 1-4.

According to a second general process (B), a compound of formula (I) may be prepared by reaction of a compound of formula (IV) with a compound of formula (XIII)

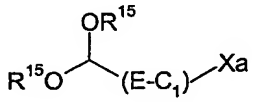


(IV) (XIII)

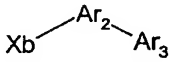
where E-C_1 ('E minus C_1') means that the chain length of group E is one carbon less than that in the resulting compound (I), under standard reductive amination

conditions, e.g. sodium triacetoxyborohydride and acetic acid in a suitable solvent, such as dichloromethane.

A compound of formula (XIII) may be prepared by reaction of a compound of formula (XIV) with a compound of formula (XV)



(XIV)



(XV)

where R^{15} is a suitable alkyl protecting group for oxygen, such as methyl, and Xa and Xb are suitable reactants to form a group X, as defined hereinbefore, followed by removal of the protecting group, under acidic conditions.

According to a third general process (C), a compound of formula (I) may be prepared by reaction of a different compound of formula (I), by well known methods. For example a compound of formula (I) where Ar_1 is substituted by C_{1-4} alkoxy may be prepared from the corresponding compound of formula (I) where the substituent is hydroxy by standard O-alkylation methods.

Compounds of formula (V), (VI), (VII), (VIII), (IX), (XI), (XIV) and (XV), are known or may be prepared by standard methods, e.g. as substantially described herein.

The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See for example 'Protective Groups in Organic Chemistry' Ed. J. F. W. McOmie (Plenum Press 1973) or 'Protective Groups in Organic Synthesis' by Theodora W Greene and P M G Wuts (John Wiley and Sons 1991).

Conventional amino protecting groups may include for example aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl groups; and acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl.

Conventional carboxylic acid protecting groups include methyl and ethyl groups.

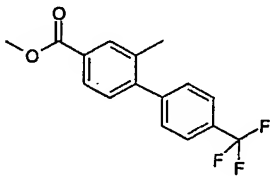
The invention is further described with reference to the following non-limiting examples.

Abbreviations :

$Pd(PPh_3)_4$- Tetrakis-(triphenylphosphine)-palladium(0), THF- Tetrahydrofuran, BF_3-Et_2O- Boron trifluoride diethyl etherate, DCM- Dichloromethane, TEA- triethylamine, CH_3CN- Acetonitrile, EtOH- Ethanol, EtOAc- Ethyl acetate, iPr_2O- Di-isopropyl ether, iPrOH- Isopropanol, Pd/C- Palladium on carbon, Et_2O- diethyl ether, Chex- cyclohexane, MeOH- Methanol, DMF- Dimethyl formamide, EDCI- 1-(3-dimethylaminopropyl)-, ethylcarbodiimide hydrochloride, HOBt- 1-Hydroxybenzotriazole, rt- Room temperature, AcOH- Acetic acid, NaOH- Sodium hydroxide, KOH- potassium hydroxide, HCl- Hydrochloric acid, AcOH- Acetic acid, NaH- Sodium hydride, Na_2SO_4- Sodium sulfate, CCl_4- Carbon tetrachloride, AIBN- 2,2'-Azobis(2-methylpropionitrile), K_2CO_3- Potassium carbonate, Na_2CO_3- Sodium carbonate, NaCl- Sodium chloride,TMAD- N,N,N',N'-tetramethylazodicarboxamide, $POCl_3$- Phosphorus oxychloride, DME-Dimethyl ether, Cs_2CO_3- Cesium carbonate, CrO3- Chromium(VI) oxide, BBr_3- Boron tribromide.

Intermediate 1

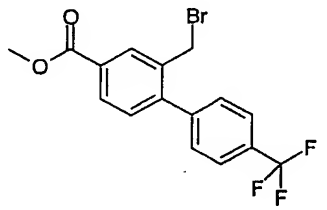
2-Methyl-4'-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester



To a solution of the 4-bromo-3-methyl-benzoic acid methyl ester (10.1g , 44 mmol) in acetonitrile (300 mL) was added $Pd(PPh_3)_4$ (1g) , a 2M Na_2CO_3 solution (40 mL) and 4-trifluoromethyl boronic acid (9.21g , 1.1 eq.). The mixture was stirred to reflux for 24 hours. After cooling, the reaction was evaporated off, diluted

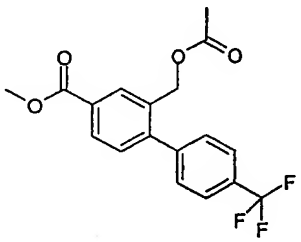
with water and extracted with DCM. The organic layer was then dried over Na_2SO_4, filtered over a silica bed and evaporated off.
The title compound (11.9 g, 40.5 mmol) was obtained as a brown solid in a 94.5% yield.
GC/MS: M^+ $C_{16}H_{13}F_3O_2$ 294

Intermediate 2
2-Bromomethyl-4'-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester



To a solution of Intermediate 1 (11.9 g, 40.5 mmol) in CCl_4 (300 mL) was added N-bromosuccinimide (10.8 g, 1.5 eq.) and AIBN (400 mg). The mixture was stirred to reflux for 48 hours and after cooling water was added. The organic layer was separated and dry over Na_2SO_4 to give after evaporation, the crude title compound as a yellow oil. The compound was used in the next step without further purification.
GC/MS: M^+ $C_{16}H_{12}BrF_3O_2$ 373

Intermediate 3
2-Acetoxymethyl-4'-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester

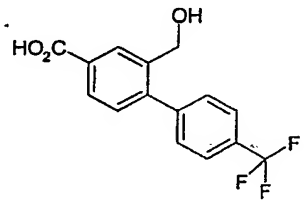


To a solution of the Intermediate 2 (16.0 g, 43 mmol) in DMF (400 mL) and acetonitrile (2 mL) was added sodium iodide (small quantity) and sodium acetate (10.6 g, 3 eq.). The reaction was stirred to reflux for 24 hours and then water

(10 mL) added and the mixture evaporated off. The residue was diluted with water and extracted with DCM. The organic layer was dried over Na_2SO_4 and evaporated off. After purification by flash chromatography, using EtOAc/Cyclohexane (10/90) as eluent, the title compound (6.0 g, 17 mmol) was obtained as white crystals in a 42% yield.
MP: 94°C

Intermediate 4

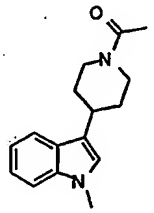
2-Hydroxymethyl-4'-trifluoromethyl-biphenyl-4-carboxylic acid



To a solution of Intermediate 3 (6.0 g, 17 mmol) in MeOH (200 mL) was added a 1 N NaOH solution (51 mL, 3 eq.).The mixture was stirred to reflux for 24 hours and then the solvant was evaporated off. The residue was treated with a 1 N HCl solution (60 mL) and the precipitate was filtered, washed with water and dried over Na_2SO_4 to give the title compound (5.0 g, 16.9 mmol) as a white powder in a quantitative yield.
LC/MS: M-H $C_{15}H_{10}F_3O_3$ 295

Intermediate 5

1-[4-(1-Methyl-1H-indol-3-yl)-piperidin-1-yl]-ethanone



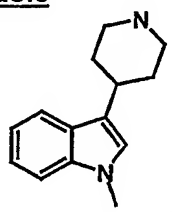
To a solution 1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethanone, (4.95 g, 20.0 mmol) in dry DMF (100 mL) was added NaH 60% (0.98 g, 1.2 eq.) and methyl iodide

(1.52 mL, 1.2 eq.). The mixture was stirred at rt for 18 hours. The mixture was evaporated off, diluted with water, extracted (DCM) and dried over Na_2SO_4 to give after evaporation, the title compound (5.2 g, 20.0 mmol) as an oil in a quantitative yield.

LC/MS: M+H $C_{16}H_{21}N_2O$ 257

Intermediate 6

1-Methyl-3-piperidin-4-yl-1H-indole



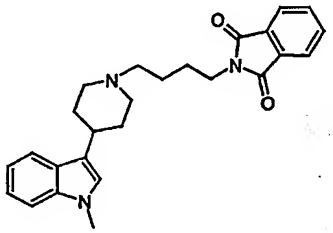
To a solution of Intermediate 5 (5.2 g, 20.0 mmol) in EtOH (100 mL) was added a $NaOH/H_2O$ (1/1) solution (14 mL) and the reaction was stirred to reflux for 16 hours. After cooling, the reaction was concentrated in vacuo, and the residue diluted with water, and extracted with DCM. The organic phase was then dried over Na_2SO_4 and evaporated off.

The title compound was obtained as a yellow solid in a quantitative yield.

GC/MS: M+ $C_{14}H_{18}N_2$ 214

Intermediate 7

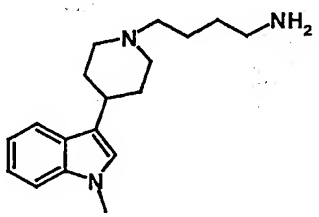
2-{4-[4-(1-Methyl-1H-indol-3-yl)-piperidin-1-yl]-butyl}-isoindole-1,3-dione



To a solution of Intermediate 6 (5.0 g, 23 mmol) in solution in acetone (200 mL) was added potassium carbonate (6.35 g, 2.0 eq.) and N-4-bromobutyl phthalimide (7.25 g, 1.1 eq.). The reaction was stirred to reflux for 16 hours. After cooling, the reaction was filtered off and the solvent was removed in vacuo.

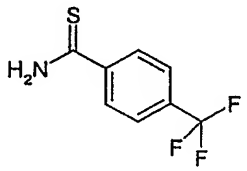
After purification by flash chromatography using DCM/MeOH (95/5) as eluent, the title compound was obtained as a yellow oil a quantitative yield.
LC/MS: M+H $C_{26}H_{27}N_3O_2$ 416

Intermediate 8
4-[4-(1-Methyl-1H-indol-3-yl)-piperidin-1-yl]-butylamine



To a solution of Intermediate 7 (9.6 g, 23 mmol) in solution in MeOH (200 mL) was added hydrazine hydrate (4.6 mL, 4.0 eq.) and the reaction stirred to reflux for 16 hours.
After evaporation under reduced pressure, the residue was taken up in water and treated with a concentrated HCl solution until pH = 3-4. The white precipitate was filtered off and washed with water. The filtrate was then treated with a concentrated NaOH solution until pH > 12. Extraction with DCM, drying over Na_2SO_4 and filtration gave the title compound (5.5 g, 19 mmol) as a yellow oil in a 83% yield.
GC/MS: M^+ $C_{18}H_{27}N_2$ 285

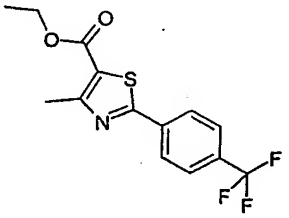
Intermediate 9
4-Trifluoromethyl-thiobenzamide



A solution of α,α,α-trifluoro-p-tolunitrile (603.5 g, 3.53 mol) in dry DMF (2 L) under N_2 was heated at 70°C and the thioacetamide (505 g, 1.9 eq.) added. The reaction mixture was treated with HCl gas for 15 minutes and was stirred at 95°C for 6 hours. This treatment was repeated 3 times and the mixture stirred at rt for

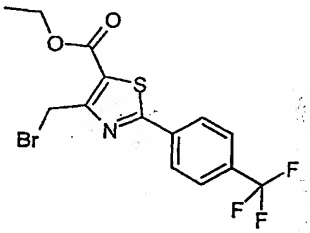
24 hours. After cooling at 0°C, water was added and the residue was extracted with diethyl ether (4 L). The organic layer was washed with water (3 L), dried over Na_2SO_4 and then evaporated off. The brownish powder was washed with pentane (3 L) to give the title compound (530.3g, 2.59 mol) as a brown solid in 73% yield.
GC/MS: M^+ $C_8H_6F_3NS$ 205

Intermediate 10
4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester



To a solution of Intermediate 9 (530.3 g, 2.59 mol) in EtOH (2.6 L) was added 2-chloro-3-oxo-butyric acid ethyl ester (465 mL, 1.3 eq.). The mixture was stirred at rt for 7 hours and at 70°C for 14 hours. After cooling at 0°C, the precipitate was filtered off and washed with cold EtOH (500 mL) to give the title compound (573.0 g, 1.89 mol) as a beige powder in a 73% yield.
^1H NMR ($CDCl_3$, 300 MHz) δ 7.9 (d, 2H), 7.6 (d, 2H), 4.3 (q, 2H), 2.65 (s, 3H), 1.25 (t, 3H).

Intermediate 11
4-Bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester

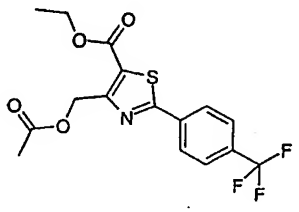


To a solution of Intermediate 10 (15.75 g, 50.0 mmol) in CCl_4 was added slowly t N-bromosuccinimide (8.9 g, 1.1 eq.) and AIBN (1 g, 10%mol). The mixture was stirred at 80°C for 3 hours , then filtered off and the filtrate evaporated. After purification by flash chromatography, using DCM/cyclohexane (60/40) as eluent, the title compound (4.9 g, 12.5 mmol) was obtained as a white solid in 25% yield.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.2 (d, 2H), 7.8 (d, 2H), 5.1 (s, 2H), 4.5 (q, 2H), 1.3 (t, 3H)

Intermediate 12

4-Acetoxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester

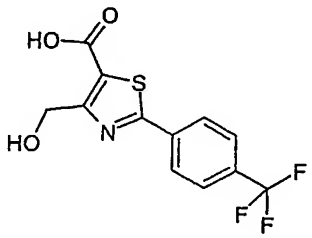


To a solution of Intermediate 11 (4.9 g, 12.5 mmol) in AcOH (15 mL) was added sodium acetate (2.0 g, 2eq.). The mixture was stirred to reflux for 14 hours, and after cooling at rt, the mixture was diluted with water (150 mL) and extracted with diethyl ether (250 mL). The organic layer was washed with a 1 N NaOH solution and dried over Na_2SO_4 and evaporated. The title compound (3.24 g, 8.7 mmol) was obtained as white crystals in a 72% yield.

MP: 82°C

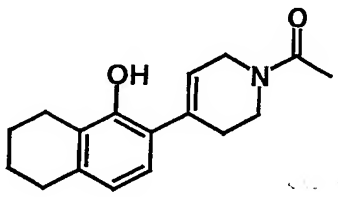
Intermediate 13

4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid



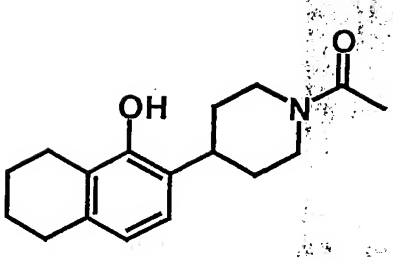
To a solution of Intermediate 12 (3.24 g, 8.7 mmol) in EtOH/H_2O (40 mL/20mL) was added NaOH (1.4 g, 4 eq.) and the mixture stirred to reflux for 2 hours. After partial evaporation, water (100 mL) was added and the mixture treated with a concentrated HCl solution to obtain pH = 1. The precipitate was filtered off, washed with water and dried to give the title compound (2.38 g, 7.8 mmol) as a white solid in 90% yield.
MP: 250-252 °C

Intermediate 14
1-[4-(1-Hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-3,6-dihydro-2H-pyridin-1-yl]-ethanone



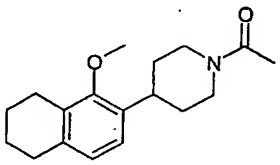
To a solution of 5,6,7,8-tetrahydro-naphthalen-1-ol (20.0 g, 0.135 mol) and 1-acetyl-4-piperidone (22.84 g, 1.2 eq.) in THF (400 mL), was added dropwise BF_3-Et_2O (68 mL, 4.0 eq). The mixture was stirred at 100°C for 2 hours, and 14 hours at room temperature. The mixture was treated with a 1N HCl solution (400 mL). The resulting solution was extracted with DCM. The organic layer was dried over Na_2SO_4 and evaporated to dryness to give an oil which was recrystallized in acetonitrile to give the title compound (24.2 g, 89 mmol) as white crystals in 66% yield.
GC/MS: M^+ $C_{17}H_{20}NO_2$ 271

Intermediate 15
1-[4-(1-Hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-ethanone



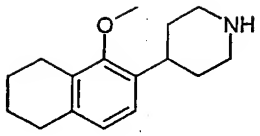
To a solution of intermediate 14 (9.4 g, 34.7 mmol) in EtOH (300 mL) was added Pd/C,10% (0.9 g) and the reaction was stirred under an atmospheric pressure of hydrogen at 25°C for 24 hours. The mixture was filtered through a bed of celite. The filtrate was evaporated under reduced pressure to give the title compound (9.6 g, 35 mmol) as a white foam.
GC/MS: M^+ $C_{17}H_{22}NO_2$ 273

Intermediate 16
1-[4-(1-Methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-ethanone



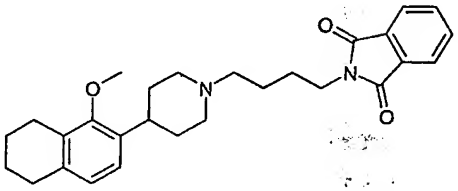
To a solution of Intermediate 15 (9.6 g, 35 mmol) in DMF (300mL) was added NaH 60% (1.6 g, 1.2 eq.) and iodomethane (22 mL , 10 eq.). The mixture was stirred at 60°C for 2 hours and water (10 mL) was added. After evaporation , the residue was taken in water and extracted with DCM and dried over Na_2SO_4 and give the title compound (10.2 g, 35 mmol) as a yellow oil in quantitative yield.
GC/MS: M^+ $C_{18}H_{24}NO_2$ 287

Intermediate 17
4-(1-Methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidine



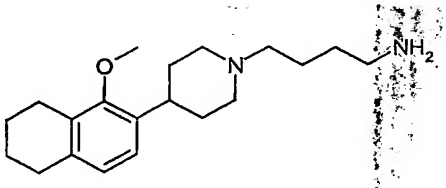
To a solution of Intermediate 16 (10.2 g, 35 mmol) in EtOH (200 mL) was added a $NaOH/H_2O$ (20 mL/20 mL) solution and the mixture was stirred to reflux for 24 hours. The solvent was evaporated off and water was added and the residue was extracted with DCM. The organic layer was dried over Na_2SO_4 and evaporated off to give the title compound (7.7 g, 31 mmol) as yellow oil in a 88.5 % yield.
GC/MS: M^+ $C_{16}H_{22}NO$ 245

Intermediate 18
2-{4-[4-(1-Methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-isoindole-1,3-dione



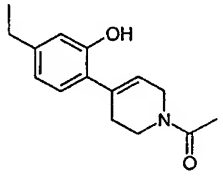
To a solution of Intermediate 17 (7.7 g, 31 mmol) in acetone (200 mL) was added K_2CO_3 (8.55 g, 2 eq.) and 4-bromobutyl-phthalimide (8.86 g, 1 eq.). The mixture was stirred to reflux for 6 hours and filtered off. The filtrate was evaporated and the residue diluted in DCM and filtered through a bed of silica to give the title compound (12.2 g, 27 mmol) as a yellow oil in 87% yield.
LC/MS: M+H $C_{28}H_{34}N_2O_3$ 447

Intermediate 19
4-[4-(1-Methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butylamine



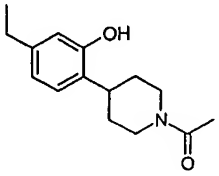
A solution of Intermediate 18 (12.2 g, 27 mmol) in MeOH (200 mL) was treated with hydrazine monohydrate (5.5 mL, 4 eq.). The resulting mixture was stirred to reflux for 16 hours. After cooling to rt, and evaporation under reduced pressure the residue was taken up in water and a 1N HCl solution was added until pH=4. Filtration gave a yellow solution which was treated with concentrated NaOH solution. Extraction with DCM ,drying over Na_2SO_4 and filtration gave the title compound (6.97 g, 22 mmol) as a yellow oil in 81% yield.
LC/MS: M+H $C_{20}H_{33}N_2O$ 317

Intermediate 20
1-[4-(4-Ethyl-2-hydroxy-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-ethanone



The same method was employed as in the preparation of intermediate 14 but starting from 3-ethyl-phenol gave the title compound as a pink solid in quantitative yield.
GC/MS: M^+ $C_{15}H_{19}NO_2$ 245

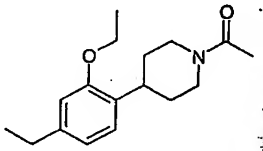
Intermediate 21
1-[4-(4-Ethyl-2-hydroxy-phenyl)-piperidin-1-yl]-ethanone



The same method was employed as in the preparation of Intermediate 15 but starting from Intermediate 20 gave the title compound as a solid in a 89% yield.

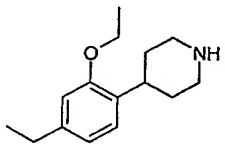
GC/MS: M^+ $C_{15}H_{21}NO_2$ 247

Intermediate 22
1-[4-(2-Ethoxy-4-ethyl-phenyl)-piperidin-1-yl]-ethanone



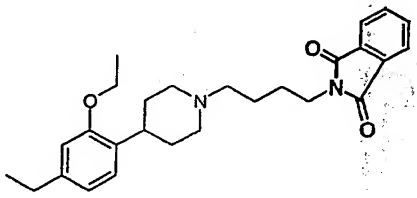
The same method was employed as in the preparation of Intermediate 16 but starting from Intermediate 21 and ethyl iodide gave the title compound as an oil in a quantitative yield .
1H NMR ($CDCl_3$, 300 MHz) δ 6.9 (d, 1H), 6.6 (m, 2H), 4.7 (m, 1H), 4.0 (q, 2H), 3.8 (m, 1H), 3.1 (m, 2H), 2.5 (m, 3H), 2.05 (s, 3H), 1.7(m, 2H), 1.50 (m, 2H), 1.35 (t, 3H), 1.1 (t, 3H).

Intermediate 23
4-(2-Ethoxy-4-ethyl-phenyl)-piperidine



The same method was employed as in the preparation of Intermediate 17 but starting from Intermediate 22 gave the title compound as a yellow oil in 94% yield .
1H NMR ($CDCl_3$, 300 MHz) δ 7.1 (d, 1H), 6.7 (d, 1H), 4.7 (d, 1H), 4.05 (q, 2H), 3.1 (m, 2H), 3.05 (m, 1H), 2.7 (td, 2H), 2.55 (q, 2H), 1.75 (m, 3H), 1.55 (m, 2H), 1.35 (t, 3H), 1.1 (t, 3H).

Intermediate 24
2-{4-[4-(2-Ethoxy-4-ethyl-phenyl)-piperidin-1-yl]-butyl}-isoindole-1,3-dione

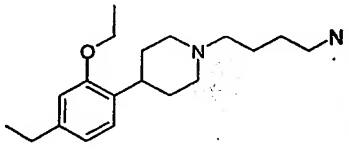


The same method was employed as in the preparation of Intermediate 18 but starting from Intermediate 23 gave the title compound as a yellow oil in 97% yield.

1H NMR ($CDCl_3$, 300 MHz) δ 7.8 (m, 2H), 7.6 (m, 2H), 7.0 (d, 1H), 6.65 (dd, 1H), 6.55 (sd, 1H), 3.95 (q, 2H), 3.65 (m, 3H), 2.95 (m, 2H), 2.8 (m, 1H), 2.5 (q, 2H), 2.4 (m, 2H), 2 (td, 2H), 1.8-1.4 (m, 8H), 1.3 (t, 3H), 1.15 (t, 3H).

Intermediate 25

4-[4-(2-Ethoxy-4-ethyl-phenyl)-piperidin-1-yl]-butylamine

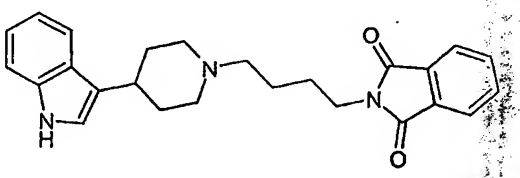


The same method was employed as in the preparation of Intermediate 19 but starting from Intermediate 24 gave the title compound as a yellow oil in 81.5% yield.

1H NMR ($CDCl_3$, 300 MHz) δ 7.1 (d, 1H), 6.7 (dd, 1H), 6.6 (s, 1H), 4.0 (q, 2H), 3.0 (bd, 2H), 2.9 (m, 1H), 2.7 (t, 2H), 2.55 (q, 2H), 2.3 (m, 2H), 2.0 (td, 2H), 1.7-1.2 (m, 10H), 1.4 (t, 3H), 1.1 (t, 3H).

Intermediate 26

2-{4-[4-(1*H*-Indol-3-yl)-piperidin-1-yl]-butyl}-isoindole-1,3-dione

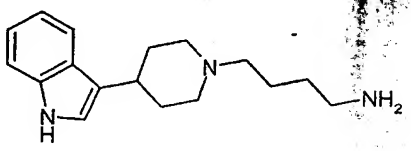


The same method was employed as in the preparation of intermediate 18 but starting from 3-piperidin-4-yl-1*H*-indole gave the title compound as white crystals in a 77% yield after recrystallisation in CH_3CN.

MP: 106-108°C

Intermediate 27

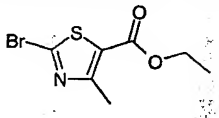
4-[4-(1*H*-Indol-3-yl)-piperidin-1-yl]-butylamine



A solution of intermediate 26 (15 g, 37.5 mmol) in EtOH (250 mL) was treated with hydrazine monohydrate (2.5 mL, 1.4 eq.). The resulting mixture was stirred at 55°C for 16 hours. After evaporation under reduced pressure the residue was taken up in acetone. Filtration and evaporation of filtrate gave the title compound (10.5 g, 38.7 mmol) as an oil in a quantitative yield.
The crude compound was used without further purification.

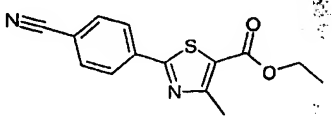
Intermediate 28

2-Bromo-4-methyl-thiazole-5-carboxylic acid ethyl ester



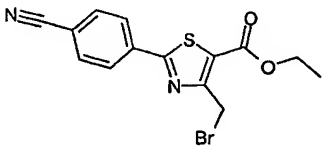
To a solution of 3-methyl-1-nitrosooxy-butane (19.8 mL, 2.1 eq) in acetonitrile (700 mL) was added at 0°C the trimethylsillyl bromide (19.6 mL , 2.1 eq). The resulting mixture was stirred at 0°C for 20 min. Then a solution of 2-amino-4-methyl-thiazole-5-carboxylic acid ethyl ester (14.0 g, 1.0 eq) in acetonitrile/EtOAc:75/25 (700 mL) was added slowly at 0°C. After stirring overnight at rt , the reaction mixture was evaporated off and purified by flash chromatography to give the title compound (13.2 g, 0.051mol) as an orange solid in a 70% yield.
GC/MS: M^+ $C_7H_8BrNO_2S$ 250
^1H NMR ($CDCl_3$, 300 MHz) δ 4.32 (q, 2H), 2.69 (s, 3H), 1.34 (t, 3H).

Intermediate 29
2-(4-Cyano-phenyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester



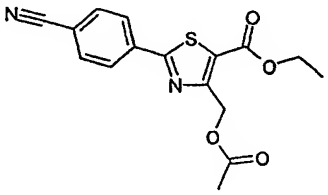
The same method was employed as in the preparation of intermediate 1 but starting from intermediate 28 (15.0 g, 0.06 mol) and 4-cyano-boronic acid (9.7 g, 1.1 eq) in DME, to give the title compound (5.2 g, 0.02 mol) as a solid in a 30% yield after purification by flash chromatography using DCM as eluent.
MP: 144°C
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, 2H), 7.73 (d, 2H), 4.36 (q, 2H), 2.78 (s, 3H), 1.38 (t, 3H).

Intermediate 30
4-Bromomethyl-2-(4-cyano-phenyl)-thiazole-5-carboxylic acid ethyl ester



The same method was employed as in the preparation of intermediate 2 but starting from intermediate 29 (2.7 g, 0.01 mol) to give the title compound (1.72 g, 4.9 mmol) as a white solid in a 49% yield after purification by flash chromatography using DCM/Hexane (70/30).
MP: 156°C

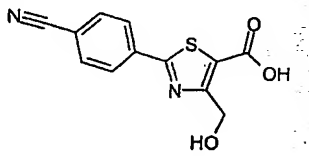
Intermediate 31
4-Acetoxymethyl-2-(4-cyano-phenyl)-thiazole-5-carboxylic acid ethyl ester



The same method was employed as in the preparation of intermediate 3 but starting from intermediate 30 (1.72 g, 5 mmol) to give the title compound (0.81 g, 2.5 mmol) as beige crystals in 50% yield after crystallisation in iPr_2O.
MP: 127°C
^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, 2H), 7.74 (d, 2H), 5.55 (s, 3H), 4.38 (q, 2H), 2.15 (s, 3H), 1.38 (t, 3H).

Intermediate 32

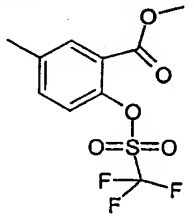
4-Hydroxymethyl-2-(4-cyano-phenyl)-thiazole-5-carboxylic acid ethyl ester



The same method was employed as in the preparation of intermediate 4 but starting from intermediate 31 (0.81 g, 2.5 mmol) to give the title compound (0.3 g, 1.15 mmol) as a beige solid in 46% yield after purification by flash chromatography using DCM/MeOH/AcOH (70/30/0.1%).
MP>250°C
LC/MS: M+H $C_{12}H_9N_2O_3S$ 261

Intermediate 33

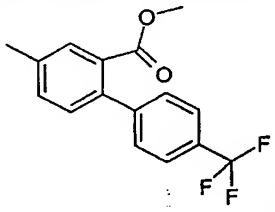
5-Methyl-2-trifluoromethylsulfonyloxy-benzoic acid methyl ester



To a solution of 2-hydroxy-5-methyl-benzoic acid methyl ester (15.0 g, 0.09 mol) in DCM was added at 0°C TEA (13.8 mL, 1.1 eq) and slowly triflic anhydride (1.1 eq). The reaction mixture was stirred at rt for 48 hours and water added. The product was extracted with DCM and the organic layer dried over Na_2SO_4,

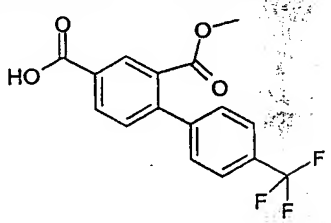
filtered off and the solvent evaporated. Purification by flash chromatography on silica gel gave the title compound as a colorless oil (4.0 g, 13.4 mmol) in 15% yield.
GC/MS: M^+ $C_{10}H_9F_3O_5S$ 298

Intermediate 34
4-Methyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid methyl ester



The same method was employed as in the preparation of intermediate 1 but starting from intermediate 33 gave the title compound as a colorless oil in 33% yield.
GC/MS: M^+ $C_{16}H_{13}F_3O_2$ 294

Intermediate 35
4'-Trifluoromethyl-biphenyl-2,4-dicarboxylic acid 2-methyl ester

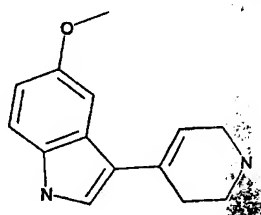


To a solution of intermediate 34 (1.3 g, 4.4 mmol) in acetic acid (20 mL) at 90°C, was added CrO_3 (2.2 g, 5 eq). The reaction mixture was stirred at 90°C for 21 hours and water added. The product was extracted with DCM, dried over Na_2SO_4, filtered off and the solvent evaporated. The title compound was obtained as green crystals (0.6 g, 1.85 mmol) in 42% yield.
LC/MS: M-H $C_{16}H_{10}F_3O_4$ 323

40

Intermediate 36

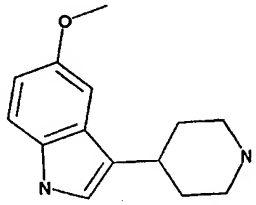
5-Methoxy-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1*H*-indole



To a solution of 5-methoxy-1*H*-indole (50.0 g, 0.34 mol) in MeOH (500 mL) under N_2 was added 4–piperidone hydrate hydrochloride (104.5 g, 2.6 eq.) and KOH (56.0 g, 3 eq.). The mixture was stirred to reflux for one night. Water (1l) was added slowly for one hour. The precipitate was filtered off and washed with water, ethanol and diethyl ether to give the title compound (51.58 g, 0.23 mol) as a yellow solid in 58% yield.
MP: 184°C

Intermediate 37

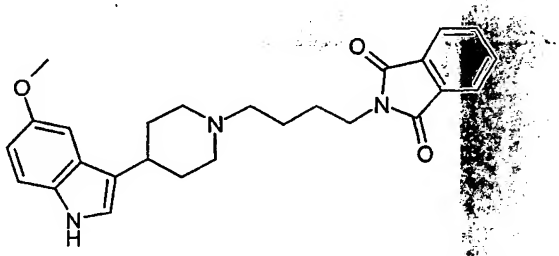
5-Methoxy-3-pyridin-4-yl-1*H*-indole



A solution of intermediate 36 (47.0 g, 0.21mol) in EtOH (500 mL), was treated with Pd/C 10% (4g) under an atmospheric pressure of hydrogen. The resulting mixture was stirred at rt for 24 hours and was filtered through a bed of celite. The filtrate was evaporated to give the title compound (45.54 g, 0.2 mol) as an orange solid in 96% yield.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.4 (d, 1H), 7.3 (bd, 1H), 7.1 (s, 1H), 7.0 (ddp, 1H), 4.0 (s, 3H), 3.4 (dd, 2H), 2.9-3.0 (m, 3H), 2.2 (m, 2H), 1.9 (m, 2H).

Intermediate 38

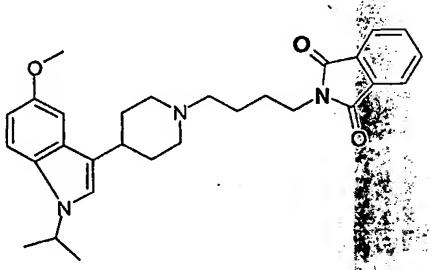
2-{4-[4-(5-Methoxy-1*H*-indol-3-yl)-piperidin-1-yl]-butyl}-isoindole-1,3-dione



The same method was employed as in the preparation of intermediate 18 but starting from intermediate 37 gave the title compound as a yellow powder in 70% yield.
MP: 155°C

Intermediate 39

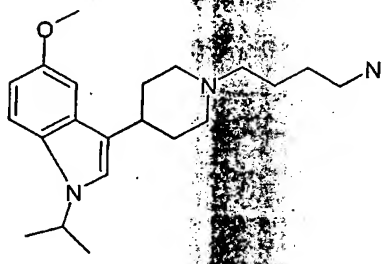
2-{4-[4-(1-Isopropyl-5-methoxy-1*H*-indol-3-yl)-piperidin-1-yl]-butyl}-isoindole-1,3-dione



The same method was employed as in the preparation of intermediate 16 but starting from intermediate 38 and the isopropyl bromide gave the title compound as an oil in a 23% yield.
LC/MS: M+H $C_{29}H_{36}N_3O_3$ 474

Intermediate 40

4-[4-(1-Isopropyl-5-methoxy-1*H*-indol-3-yl)-piperidin-1-yl]-butylamine



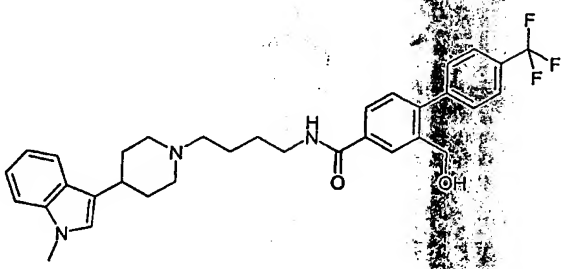
The same method was employed as in the preparation of intermediate 27 but starting from intermediate 39 gave the title compound as a foam oil in quantitative yield.

The crude compound was used in the next step without further purification.

EXAMPLES

Example 1 :

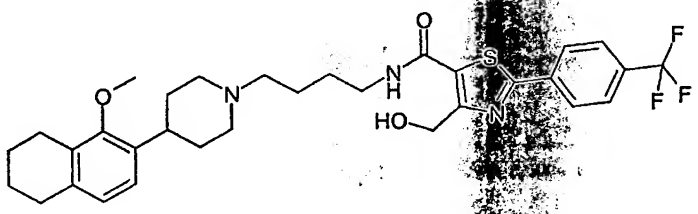
2-Hydroxymethyl-4'-trifluoromethyl-biphenyl-4-carboxylic acid {4-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-butyl}-amide



A solution of intermediate 4 (2.0 g, 7 mmol) in DMF was treated with intermediate 8 (2.0 g, 1.0 eq.), EDCI (2.02 g, 1.5 eq.), HOBT (1.43 g, 1.5 eq.) and TEA (1.5 mL, 1.5 eq.). The resulting mixture was stirred for 24 hours at rt, and evaporated off. The residue was diluted with DCM and washed with water and with a 1N NaOH solution. The organic layer was dried over Na_2SO_4 and the solvent evaporated. After purification by flash chromatography using

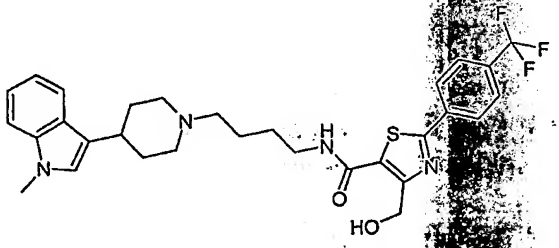
DCM/MeOH (95/5) as eluent, the title compound (2.3 g, 4 mmol) was obtained as white crystals in 58% yield after crystallisation from acetonitrile.
MP: 177°C
LC/Tof : ES^+ 564.2867 5.3 ppm

Example 2 :
4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid {4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide



The same method was employed as in the preparation of example 1 but starting from the intermediate 13 and intermediate 19 gave the title compound as white crystals in a 36% yield after recrystallisation in EtOH.
MP: 179-180°C
^1H NMR ($CDCl_3$, 300 MHz) δ 8.6 (s, 1H), 8.0 (d, 2H), 7.6 (d, 2H), 6.9 (d, 1H), 6.7 (d, 2H), 4.9 (s, 2H), 3.6 (s, 3H), 3.4 (m, 2H), 3.0 (m, 2H), 2.8 (m, 1H), 2.6 (m, 4H), 2.3 (m, 2H), 2.0 (m, 2H), 1.6 (m, 12H)

Example 3 :
4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid {4-[4-(1-methyl-1*H*-indol-3-yl)-piperidin-1-yl]-butyl}-amide



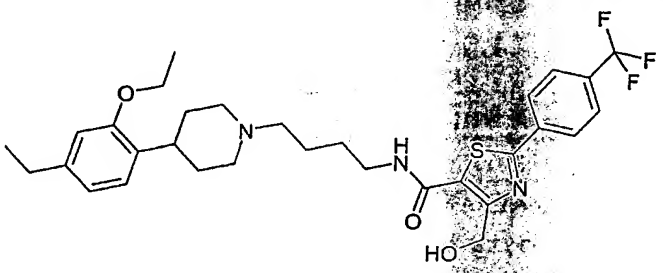
The same method was employed as in the preparation of example 1 but starting from intermediate 13 and intermediate 8 gave the title compound as a yellow powder in a 38% yield after recrystallisation in CH_3CN.

MP: 160°C

LC/Tof: ES^+ 571.2358 0.5ppm

Example 4 :

4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid {4-[4-(2-ethoxy-4-ethyl-phenyl)-piperidin-1-yl]-butyl}-amide



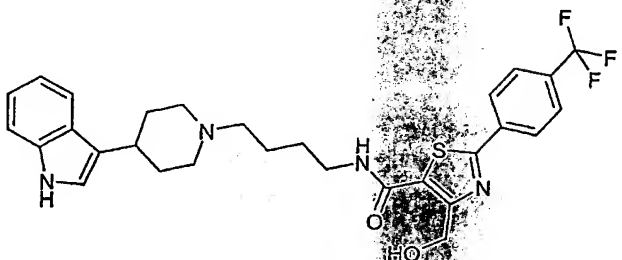
The same method was employed as in the preparation of example 1 but starting from intermediate 13 and intermediate 25 gave the title compound as beige crystals in a 25% yield after recrystallisation in CH_3CN.

MP: 150°C

LC/MS: M+H $C_{31}H_{39}F_3N_3O_3S$ 590

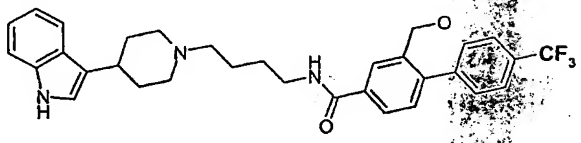
Example 5 :

4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid {4-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-butyl}-amide



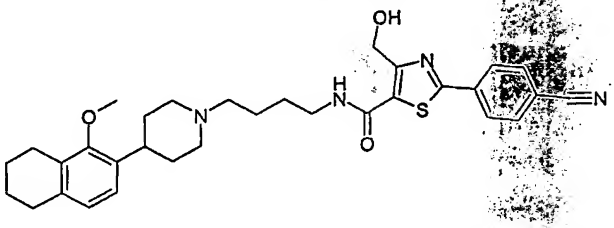
The same method was employed as in the preparation of example 1 but starting from intermediate 27 and intermediate 13 gave the title compound as yellow crystals in a 31% yield after recrystallisation in CH_3CN/EtOH.
MP: 235°C
LC/Tof: ES^+ 557.2158 7.1ppm

Example 6 :
3-Hydroxymethyl-4'-trifluoromethyl-biphenyl-4-carboxylic acid {4-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-butyl}-amide



The same method was employed as in the preparation of example 1 but starting from intermediate 27 and intermediate 4 gave the title compound as white crystals in a 42% yield after crystallisation in DMF.
MP: 255°C
LC/Tof: ES^+ 550.2725 8.0ppm

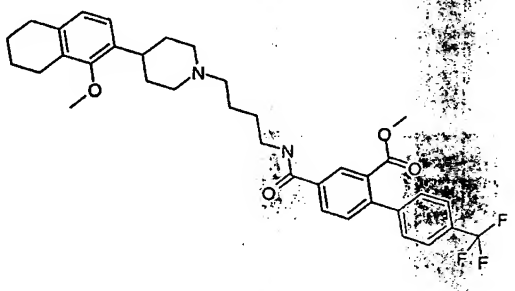
Example 7:
2-(4-Cyano-phenyl)-4-hydroxymethyl-thiazole-5-carboxylic acid {4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide



The same method was employed as in the preparation of example 1 but starting from intermediate 32 and intermediate 19 gave the title compound as beige crystals in a 8% yield after crystallisation in ethyl acetate.

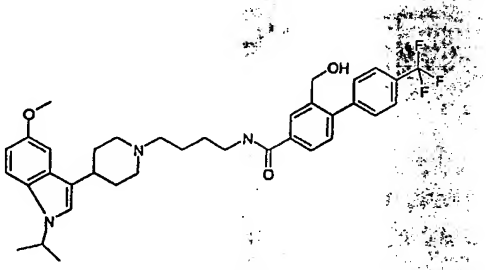
MP: 212°C
LC/MS : M-H $C_{32}H_{37}N_4O_3S$ 557

Example 8:
4-{4-[4-(1-Methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butylcarbamoyl}-4'-trifluoromethyl-biphenyl-2-carboxylic acid methyl ester



The same method was employed as in the preparation of example 1 but starting from intermediate 35 and intermediate 19 gave the title compound as white crystals in a 51% yield after crystallisation from $iPrO_2$.
MP: 132°C
LC/Tof : ES^+ 623.3063 5.3 ppm

Example 9:
2-Hydroxymethyl-4'-trifluoromethyl-biphenyl-4-carboxylic acid {4-[4-(1-isopropyl-5-methoxy-1*H*-indol-3-yl)-piperidin-1-yl]-butyl}-amide



The same method was employed as in the preparation of example 1 but starting from intermediate 40 and intermediate 4 gave the title compound as a white solid in a 39% yield after crystallisation in hexane.
MP: 90-100°C
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (s, 1H), 7.76 (d, 1H), 7.60 (d, 2H), 7.38 (d, 2H), 7.25-7.14 (m, 2H), 7.02 (s, 1H), 6.86 (s, 2H), 4.53 (s, 2H) 3.83 (s, 3H), 3.47 (m, 2H), 3.02 (m, 2H), 2.75 (m, 1H), 2.41 (m, 2H), 2.13-1.97 (m, 4H), 1.67 (m, 4H), 1.41 (d, 6H).

Biological Assays

In Vitro Assay :

$HepG_2$ cells, stably transfected with a construct comprising the the LDL-r promoter and the luciferase reporter gene, were seeded at 50.000 cells/well in 96 well plates. After 1 day, cells were incubated with compounds for 24 hours in RPMI medium containing 2% of lipoprotein-deficient serum. Compounds were tested from 10^{-6}M to 10^{-9}M.Cell lysates were prepared and the luciferase activity was measured by the luciferase assay system (Promega). Induction of luciferase activity was calculated taking untreated cells as control and ED_{50} of each compounds was determined compared to the ED_{50} of an internal standard.

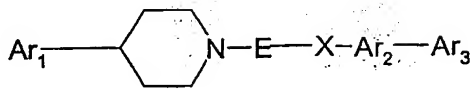
In Vivo Assay :

Compounds were prepared for oral administration by milling with 0.5% hydroxypropylmethylcellulose and 5% Tween 80. Hamsters were fed for 2 weeks with a diet containing 0.2% of cholesterol and 10% of coconut oil. Then compounds were administered once a day for 3 days, from 20 to 0.2mg/kg. Plasma lipid levels including total cholesterol, VLDL/LDL cholesterol, VLDL/LDL triglycerides and HDL-cholesterol were determined after ultracentrifugation (density 1.063g/ml to separate VLDL/LDL fraction and HDL fraction) using the Biomerieux enzymatic kit. Reductions in VLDL/LDL cholesterol and TG plasmatic levels were calculated taking solvent treated animals as control and ED_{50} of each compound was determined.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, the following claims:

CLAIMS

1. A compound of formula (I)



(I)

wherein

Ar_1 represents

(iii) phenyl, naphthyl, or phenyl fused by a C_{3-8}cycloalkyl , or

(iv) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, provided that at least one ring is aromatic,

where Ar_1 optionally bears 1-4 groups independently represented by R^1 ;

R^1 is selected from halogen, -O-(C_{0-4} alkylene)-R^2 or –(C_{0-4}alkylene)-R^2, where each alkylene group may additionally incorporate an oxygen in the chain, with the proviso that there are at least two carbon atoms between any chain heteroatoms ;

R^2 represents

(v) hydrogen, C_{1-4} perfluoroalkyl, C_{1-4}perfluoroalkoxy,

(vi) phenyl, phenyl fused by a C_{3-8}cycloalkyl , naphthyl or a 5- or 6-membered heteroaromatic group, optionally substituted by one or two groups independently selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino and di-C_{1-4} alkylamino,

(vii) C_{3-8}cycloalkyl or a monocyclic heterocyclyl radical containing a total of 3-7 ring atoms, wherein said radical contains a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur,

wherein said radical may be independently saturated, partially unsaturated, or aromatic, and where the C_{3-8}cycloalkyl or a monocyclic heterocyclyl may bear one or two groups independently selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino and di-C_{1-4} alkylamino, or

(viii) amino, C_{1-4} alkylamino or di-C_{1-4}alkylamino;

Ar_2 represents phenyl or a 5-6 membered heteroaromatic group or a bicyclic heteroaromatic group, where each group is substituted by 1-4 groups independently selected from the group consisting of: $(CH_2)_nOH$ and $C(O)O(CH_2)_mCH_3$, wherein n is 1-4 and m is 0-4;

Ar_3 represents

(iii) phenyl, naphthyl, or phenyl fused by a C_{3-8}cycloalkyl,

(iv) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, providing that at least one ring is aromatic,

where Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: hydroxy, alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkenyloxy, C_{1-4} perfluoroalkoxy, C_{1-4} acylamino or an electron withdrawing group selected from the list consisting of: nitrile, nitro, C_{1-4}, C_{1-4} perfluoroalkyl, C_{1-4} acyl , C_{1-4} alkoxycarbonyl, aminocarbonyl, C_{1-4} alkylaminocarbonyl; di-C_{1-4} alkylaminocarbonyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylaminosulfonyl and di-C_{1-4} alkylaminosulfonyl, C_{1-4} alkylsulfonyl and C_{1-4}alkylsulfoxy;

E represents -C_{1-6} alkylene-;

X represents -CON(H or C_{1-4}alkyl)- or –N(H or C_{1-4}alkyl)CO-;

or a physiologically acceptable prodrug, salt or solvate thereof.

2. A compound selected from

2-Hydroxymethyl-4'-trifluoromethyl-biphenyl-4-carboxylic acid {4-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-butyl}-amide;

4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid {4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphtalen-2-yl)-piperidin-1-yl]-butyl}-amide;

4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid {4-[4-(1-methyl-1*H*-indol-3-yl)-piperidin-1-yl]-butyl}-amide;

4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid {4-[4-(2-ethoxy-4-ethyl-phenyl)-piperidin-1-yl]-butyl}-amide;

4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid {4-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-butyl}-amide;

2-Hydroxymethyl-4'-trifluoromethyl-biphenyl-4-carboxylic acid {4-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-butyl}-amide;

2-(4-Cyano-phenyl)-4-hydroxymethyl-thiazole-5-carboxylic acid {4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphtalen-2-yl)-piperidin-1-yl]-butyl}-amide;

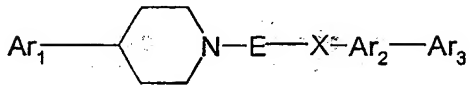
4-{4-[4-(1-Methoxy-5,6,7,8-tetrahydro-naphtalen-2-yl)-piperidin-1-yl]-butylcarbamoyl}-4'-trifluoromethyl-biphenyl-2-carboxylic acid methyl ester;

2-Hydroxymethyl-4'-trifluoromethyl-biphenyl-4-carboxylic acid {4-[4-(1-isopropyl-5-methoxy-1*H*-indol-3-yl)-piperidin-1-yl]-butyl}-amide;

or a physiologically acceptable prodrug, salt or solvate thereof.

ABSTRACT

The invention relates to a compound of formula (I)



(I)

wherein

Ar_1 represents

(v) phenyl, naphthyl, or phenyl fused by a C_{3-8}cycloalkyl , or

(vi) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, provided that at least one ring is aromatic,

where Ar_1 optionally bears 1-4 groups independently represented by R^1 ;

R^1 is selected from halogen, -O-(C_{0-4} alkylene)-R^2 or –(C_{0-4}alkylene)-R^2, where each alkylene group may additionally incorporate an oxygen in the chain, with the proviso that there are at least two carbon atoms between any chain heteroatoms ;

R^2 represents

(ix) hydrogen, C_{1-4} perfluoroalkyl, C_{1-4}perfluoroalkoxy,

(x) phenyl, phenyl fused by a C_{3-8}cycloalkyl , naphthyl or a 5- or 6-membered heteroaromatic group, optionally substituted by one or two groups independently selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino and di-C_{1-4} alkylamino,

(xi) C_{3-8}cycloalkyl or a monocyclic heterocyclyl radical containing a total of 3-7 ring atoms, wherein said radical contains a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur,

wherein said radical may be independently saturated, partially unsaturated, or aromatic, and where the C_{3-8}cycloalkyl or a monocyclic heterocyclyl may bear one or two groups independently selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino and di-C_{1-4} alkylamino, or

(xii) amino, C_{1-4} alkylamino or di-C_{1-4}alkylamino;

Ar_2 represents phenyl or a 5-6 membered heteroaromatic group or a bicyclic heteroaromatic group, where each group is substituted by 1-4 groups independently selected from the group consisting of: $(CH_2)_nOH$ and $C(O)O(CH_2)_mCH_3$, wherein n is 1-4 and m is 0-4;

Ar_3 represents

(v) phenyl, naphthyl, or phenyl fused by a C_{3-8}cycloalkyl,

(vi) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, providing that at least one ring is aromatic,

where Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: hydroxy, alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkenyloxy, C_{1-4} perfluoroalkoxy, C_{1-4} acylamino or an electron withdrawing group selected from the list consisting of: nitrile, nitro, C_{1-4}, C_{1-4} perfluoroalkyl, C_{1-4} acyl , C_{1-4} alkoxycarbonyl, aminocarbonyl, C_{1-4} alkylaminocarbonyl; di-C_{1-4} alkylaminocarbonyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylaminosulfonyl and di-C_{1-4} alkylaminosulfonyl, C_{1-4} alkylsulfonyl and C_{1-4}alkylsulfoxy;

E represents -C_{1-6} alkylene-;

X represents -CON(H or C_{1-4}alkyl)- or –N(H or C_{1-4}alkyl)CO-;

or a physiologically acceptable prodrug, salt or solvate thereof.